Armed Forces College of Medicine

AFCM

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Gastrointestinal and metabolism module

Clinical Integrated Cases
Session 3

Basic Science Principles for Clinical Reasoning

1- Critical thinking

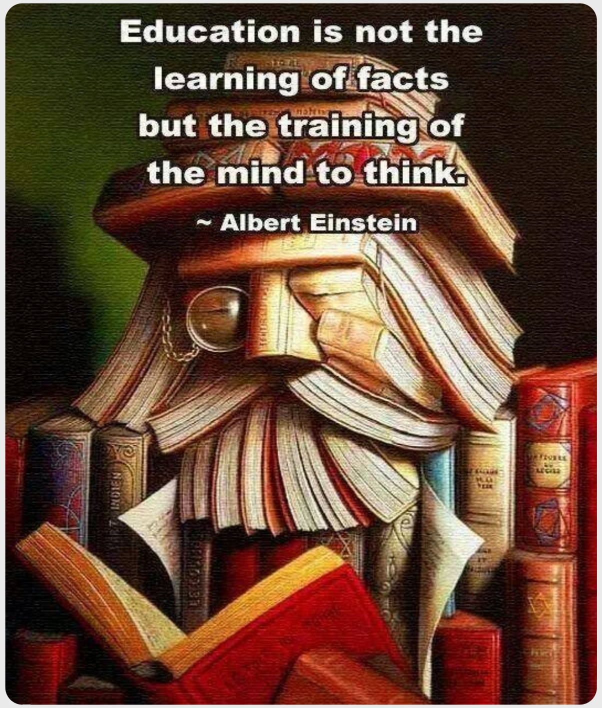
2- Introduction to common forms of disease

3- **Problem solving:**

Apply basic knowledge in a realistic clinical scenario.

4- Interpersonal skills-(share and apply your knowledge)

communication…patient safety


Education is not the learning of facts but the training of the mind to think.
~ Albert Einstein

Case: I have an abdominal pain

Presented by
Prof. Drs. Manal Hassan, Lamiaa Foad, Yasser

Sharing departments

- Gastroenterology department
- Physiology department
- Anatomy department
- Histology department
- Pathology department
- Pharmacology department
- Microbiology department

I have an abdominal pain

Laila is a 58-year-old woman. She is married and has 3 offsprings youngest 30 years old. She presents with **fatigue**, **malaise** and **anorexia**. During the last 6 months, she occasionally suffered nausea and loss of appetite and abdominal pain. No change in bowel habi stool color

Past History:

She did have a blood transfusion several years ago following the birth of her third child.

Drug history: She denies intravenous drug use. She is on ramipril 5 mg/day for the last 3 years to treat primary hypertension.

I have an abdominal pain

General Examination

Patient is overweight with BMI: 30

Vital data:

Blood pressure: 130/80 mmHg

Pulse: 88 beat/min

Temperature: 36.8 ^{0}C

Respiratory rate: 18/min

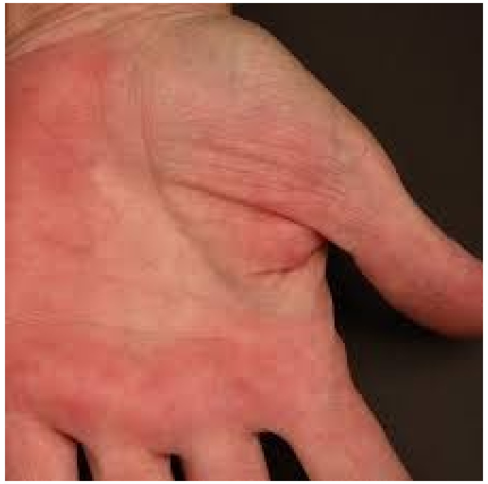
Complexion: no jaundice, no pallor, or cyanosis

Jugular venous pressure: normal

No flapping tremors,

Mild pitting lower limb edema,

Palmar erythema



I have an abdominal pain

Local Examination

Inspection: generalized bulge

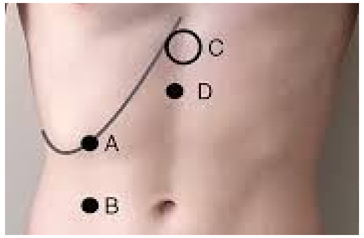
Superficial palpation: no superficial masses, tenderness, or rigidity.

Deep palpation: **mildly enlarged right liver lobe** 17 cm in MCL, **firm** in consistency, **sharp border**, smooth surface.

No splenomegaly.

Percussion: **Moderate ascites**

Auscultation: Normal intestinal sounds



wiki How to Know if You Have an Enlarged Liver

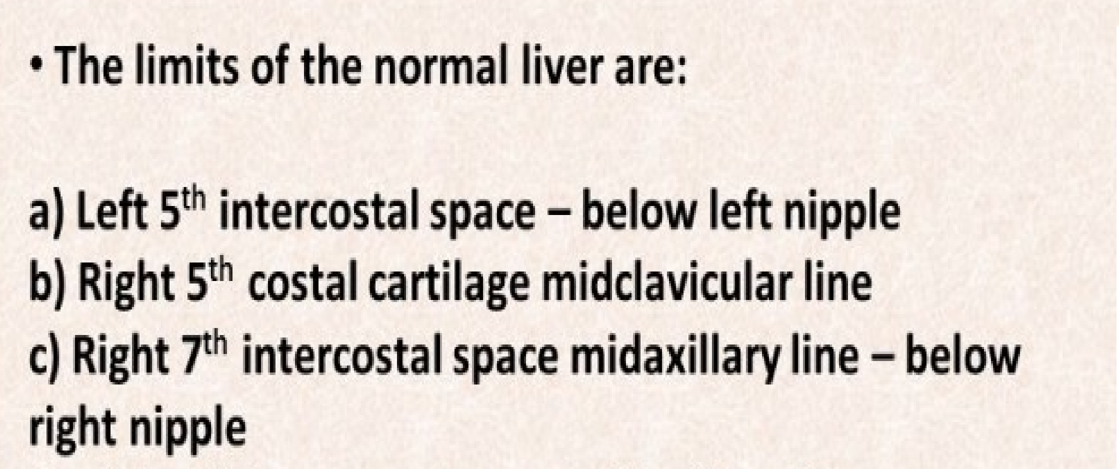
1- a-List the patient problems

b- What could be the possible causes of Laila’s symptoms?

- **Portal hypentensive gastropathy.**
- **Peptic ulcer disease.**
- **HCC (hepatocellular carcinoma).**
- **SBP (spontaneous bacterial peritonitis).**
- **Portal vein thrombosis.**

2- Describe on anatomical basis why the liver is considered enlarged?

SURFACE ANATOMY OF LIVER

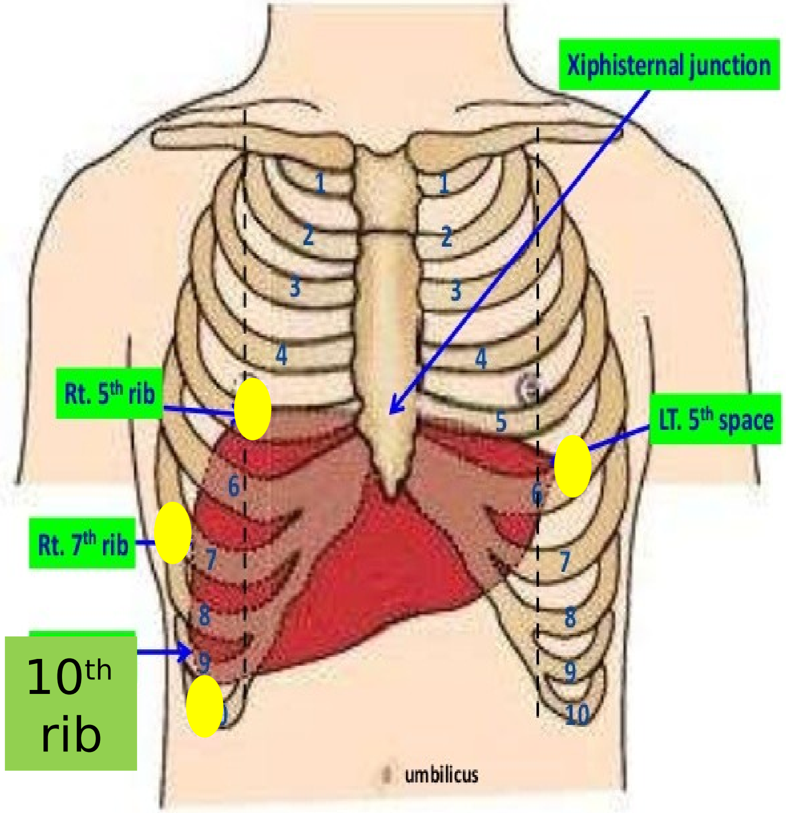


- The limits of the normal liver are:

a) Left 5th intercostal space – below left nipple
b) Right 5th costal cartilage midclavicular line
c) Right 7th intercostal space midaxillary line – below right nipple

- The right border:

from point 7th rib down to one cm below the right 10th rib in the midaxillary line.



She presents with **fatigue**, **malaise** and **anorexia**

Explain

3- What investigations do you suggest to reach a diagnosis?

Welcome Back

I have an abdominal pain

The doctor asked for the following investigations:

- CBC
- AST and ALT
- Serum albumin
- Serum bilirubin
- Alkaline phosphatase
- Gamma-glutamyl transferase
- INR
- Abdominal ultrasound

I have an abdominal pain

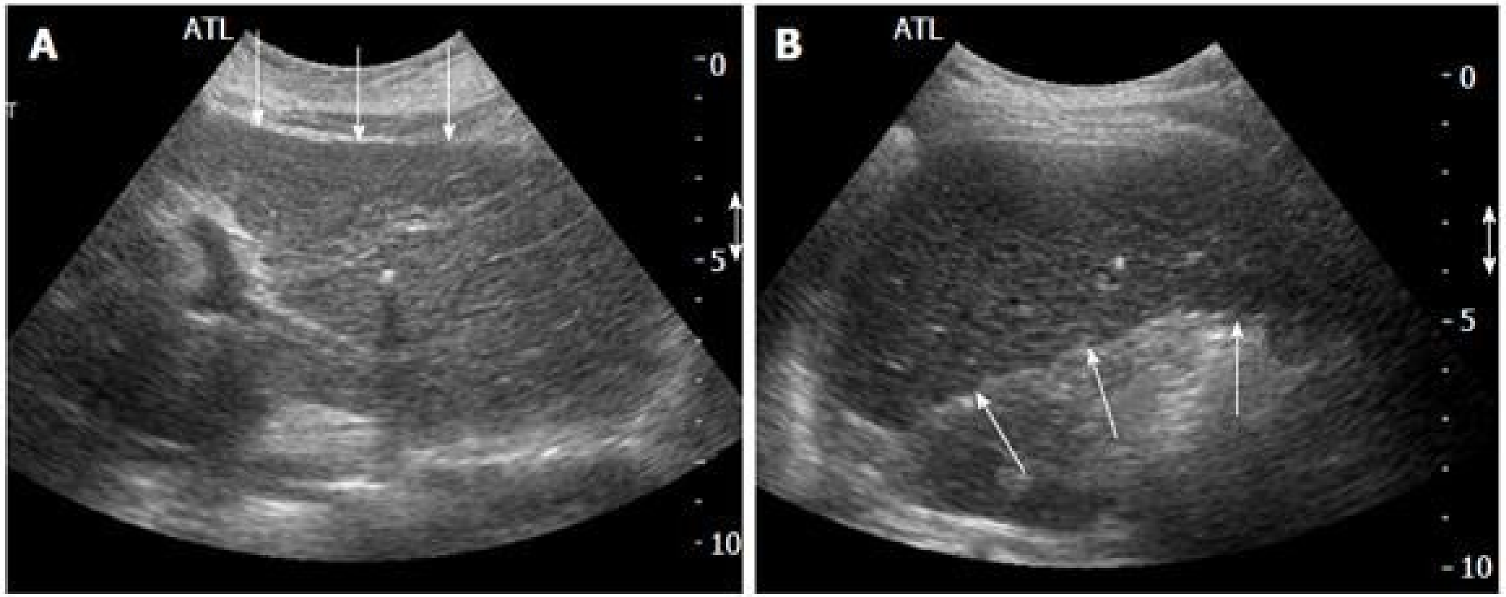
Results showed

- **Bilirubin level total** 1.3 mg/dl (up to 1.1)
- **Direct bilirubin**: 0.4mg/dl (up to 0.2)
- **Albumin** 2.8 g/dl (3.5-5.5)
- **ALT** 77 U/L (10 - 35)
- **AST** 90 U/L (10 - 35)
- **Alkaline phosphatase** 299U/l (up to 290)
- **Gamma-glutamyl transferase** 70 U/L (up to 37)
- **International normalization ratio** INR: 1.5
- **CBC**
  - Hemoglobin 13 g/dl
  - RBCs: normocytic normochromic cells
  - WBC: 6000/cmm
  - Platelet count: 87,000/cmm

I have an abdominal pain

Abdominal ultrasound showed:

- **Enlarged, Coarse cirrhotic liver**, portal vein dilated
- splenomegaly
- moderate **ascites**



4- What is your diagnosis?

Justify your answers

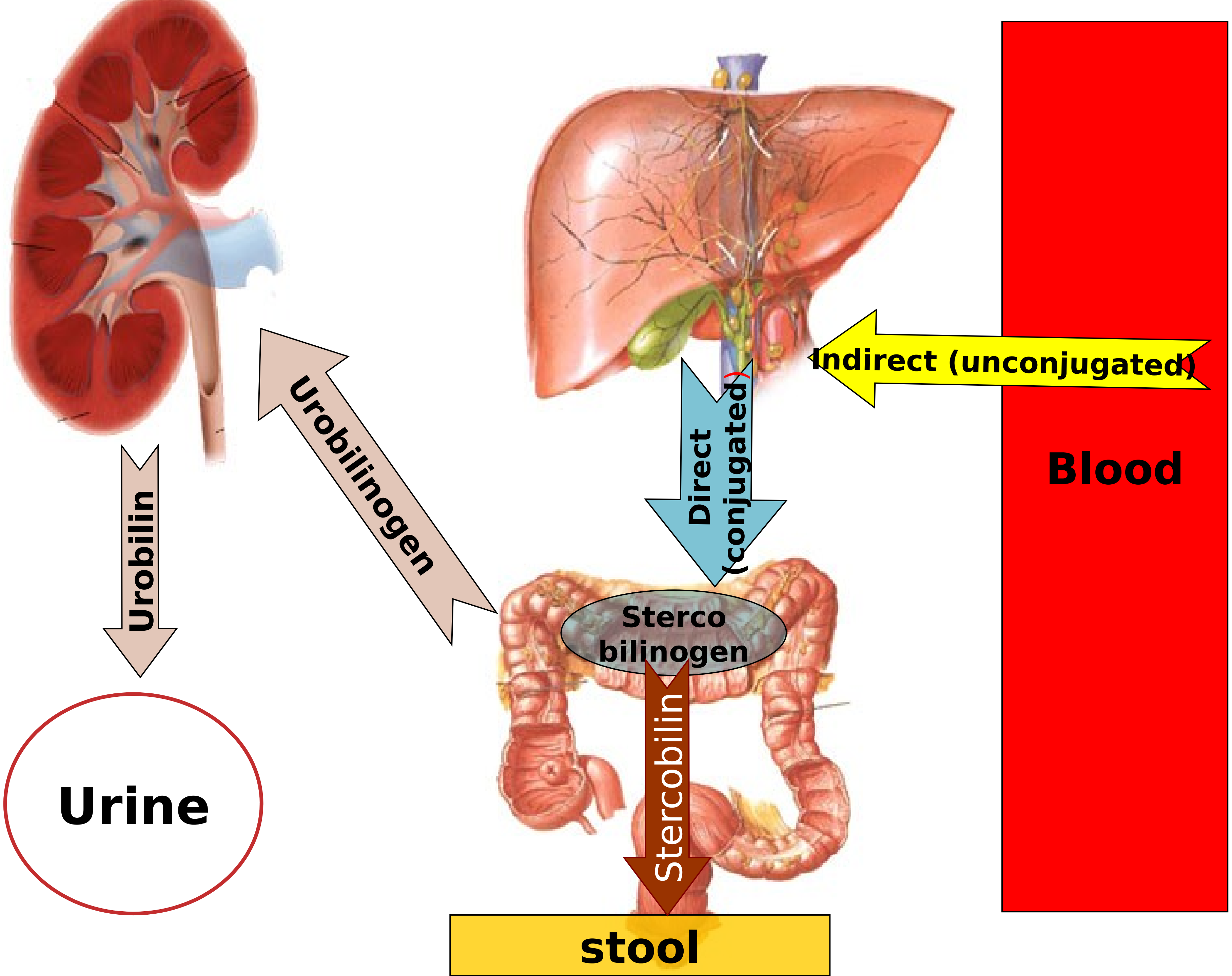
Provisional diagnosis

Liver cirrhosis for DD, decompensated (Child B) complicated BY PORTAL HYPERTENSION

Bilirubin level total 1.3 mg/dl (up to 1.1)

Direct bilirubin: 0.4mg/dl (up to 0.2)

Explain the biochemical significance of measuring bilirubin in Laila



Blood

Indirect (unconjugated)

Direct (conjugated)

Sterco bilinogen

Stercobilin

stool

Urobilinogen

Urobilin

Urine

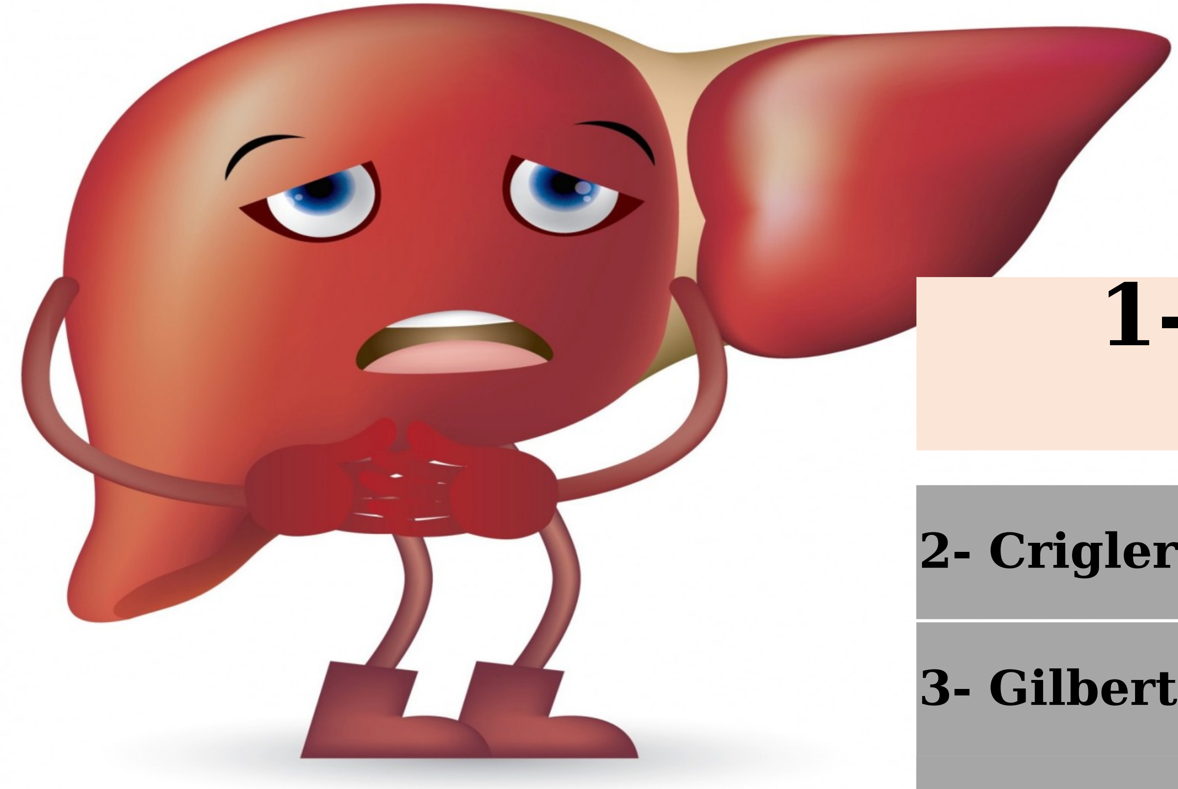
Hepatic Jaundice

Bilirubin

Unconjugated bilirubin

Conjugated bilirubin

B- Hepatic Jaundice



1- Hepatocellular damage

2- Crigler-Najjar syndromes I & II

3- Gilbert syndrome

4- Dubin–Johnson syndrome

5- Rotor syndrome

1- Hepatocellular damage

Causes:

Toxins, drugs, hepatitis viruses and cirrhosis

Damage to liver cells and decreased conjugation capacity

Increase of UCB levels the blood

Inflammatory oedema of hepatocytes with compression of the intracellular canaliculi "mild obstruction"

Increase of CB levels the blood

5- Describe the biochemical assessment of liver function.

Liver tests can be classified based on the major functions of liver:

- **Synthetic function**
- **Excretory function**
- **Test of integrity**
- **Detoxification**

Liver tests can be classified based on the major functions of liver:

Synthetic function	PT & serum albumin
Excretory function	Bilirubin
Test of integrity	ALT & AST, ALP
Detoxification	Determination of blood NH3

Results of investigations showed:

- **Bilirubin level total** 1.3 **mg/dl**
- **Direct bilirubin:** 0.4 **mg/dl**
- **Albumin:** 2.8 **g/dl**
- **ALT 77 U/L (10 - 35)**
- **AST 90 U/L (10 - 35)**
- **INR: 1.5**

6- Based on the above-mentioned results, What are the impaired and the preserved liver functions in Laila?

Functions of the liver are:

1) **Metabolic =**

- ✓ glucostate organ
- ✓ plasma protein synthesis
- ✓ synthesis of cholesterol and bile salt.
- ✓ storage of vitamins and minerals ?? (vit B12,A,D , iron and copper).

2) **Secretion** of bile salts

1) **Excretory function** is affected as there is mild elevation in total bilirubin and direct bilirubin

2) **Plasma protein formation** is abnormal as indicated by decreased level of albumin and increase INR (function of prothrombin)

3) **Elevated liver enzymes** indicate inflammation of liver cells. **Elevation of ALT occurs in most cases of cirrhosis**

7- What are the possible causes of Liver cirrhosis in Laila?

Differential diagnosis: Causes of cirrhosis:

- Viral Hepatitis:
  - Hepatitis C.
  - Hepatitis B.
  - Hepatitis B with hepatitis D
- Alcoholic liver disease
- NAFLD
- Metabolic:
  - Hemochromatosis
  - Wilson disease
  - Alpha-1 antitrypsin deficiency

- Cryptogenic causes (18%) - Many cases actually are due to NAFLD
- Autoimmune causes:
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
- Granulomatous disease – e.g: sarcoidosis

Type IV glycogen storage disease

Drug-induced liver disease - e.g: methotrexate, alpha methyldopa, amiodarone

Vascular: Venous outflow obstruction e.g: Budd-Chiari syndrome, veno-occlusive disease

Chronic right-sided heart failure

Drug history: She denies intravenous drug use.
She is on ramipril 5 mg/day for the last 3 years to treat primary hypertension.

Is the drug history important in Laila?

What further needed investigations to reach the cause of cirrhosis in Laila?

I have an abdominal pain

Further investigations

- HBsAg
- HCV Ab
- HCV-RNA-PCR

Results showed:

HBsAg: negative

HCV Ab: positive

HCV-RNA-PCR: 233411 IU/ml (detection limit : 15 IU/ml)

Definitive diagnosis

- **Liver cirrhosis post hepatitic Chronic HCV, decompensated (Child B) complicated by portal hypertension.**

- HBsAg
- HCV Ab
- HCV-RNA-PCR

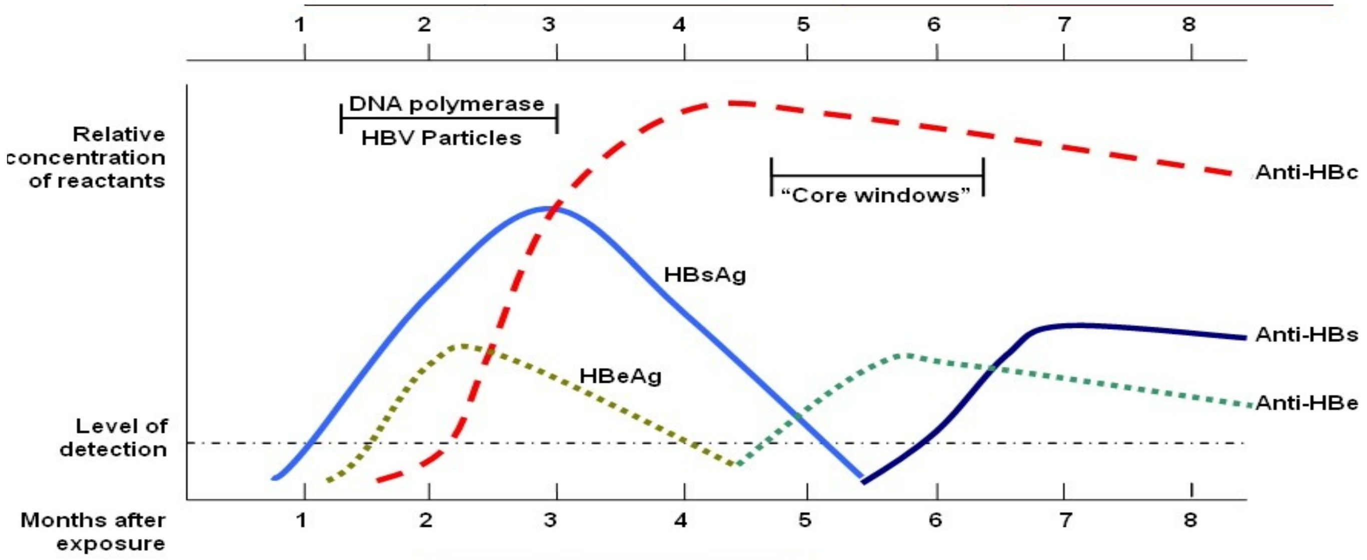
8- Explain the principal of these tests

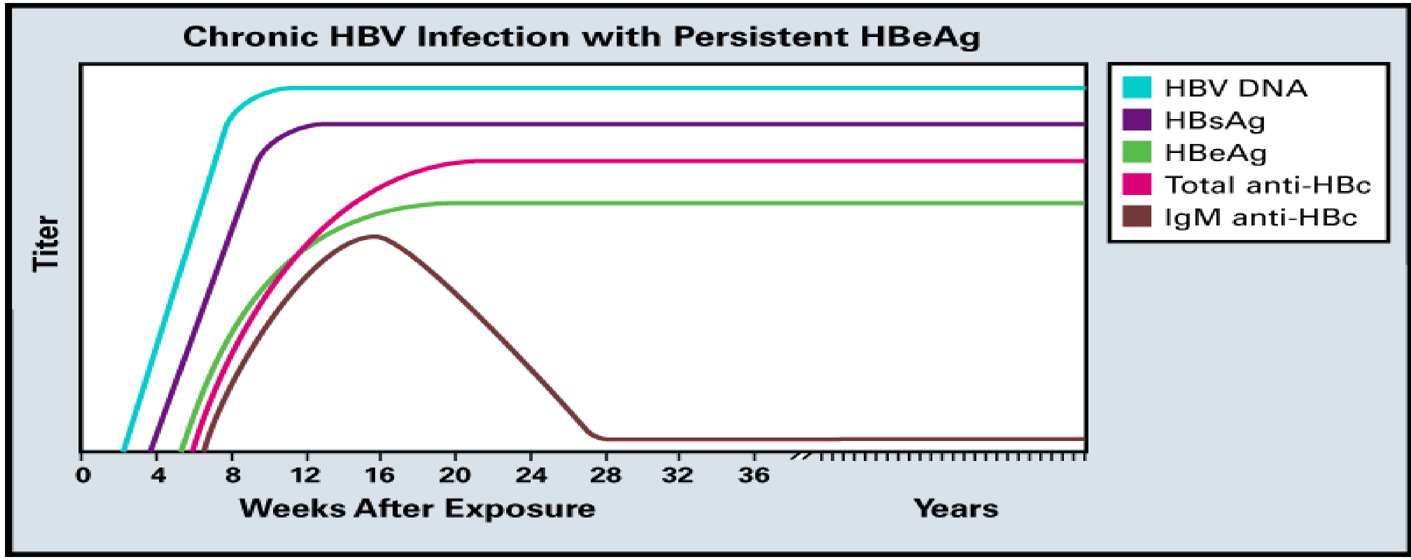
HBsAg

a. Time of detection (TOD): ↓ in 3 months

Disappears after **6 months**

except in chronicity





Diagnosis of HCV

A-Detection of Abs: By Rapid Ab detection test : screening test for Ab

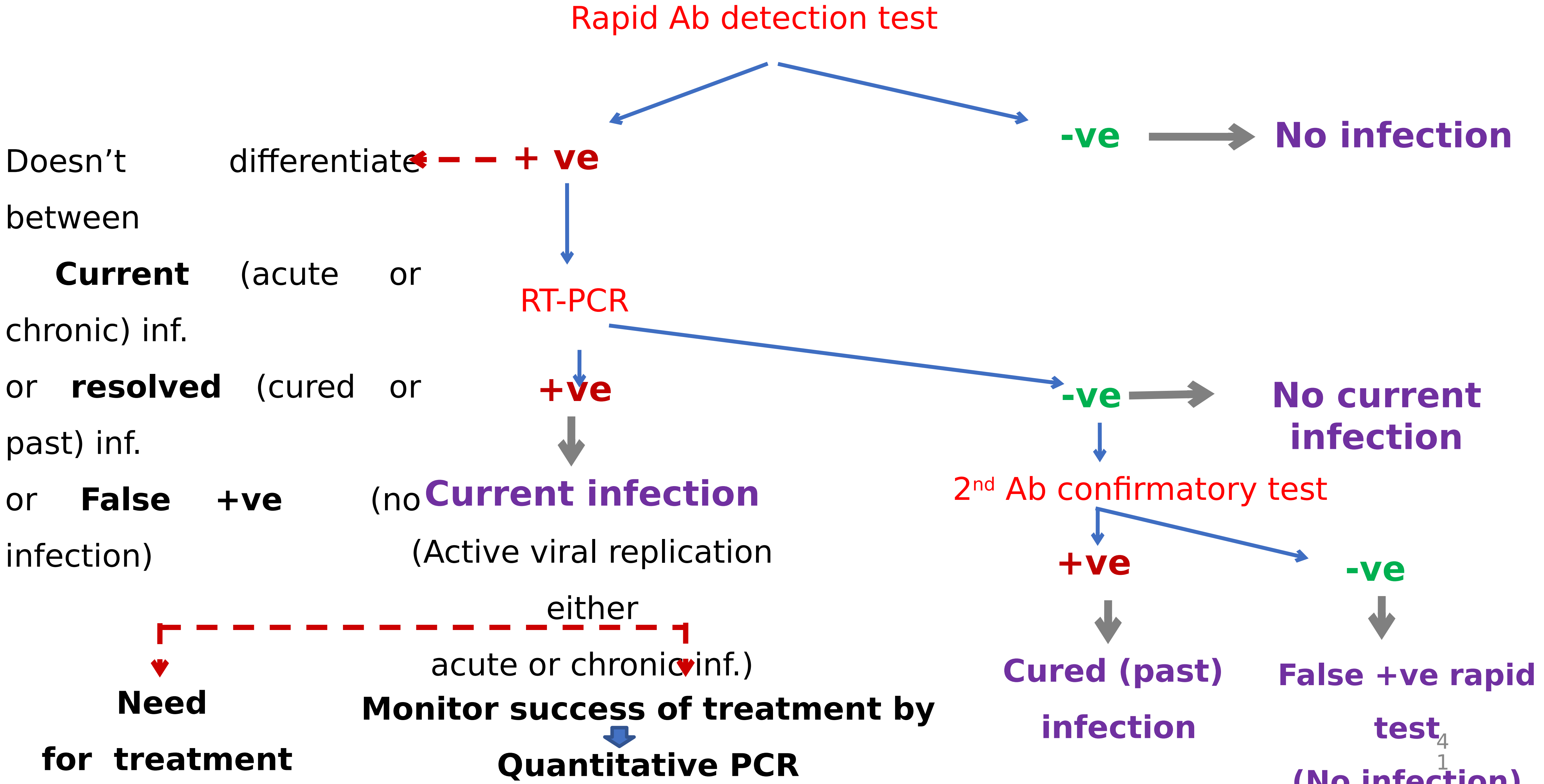
(false +ve result may occur due to cross reacting Abs)

- **2nd confirmatory Ab assay**

B- RT(reverse transcription)-PCR

Detection of viral RNA in blood: signifies c**urrent infection and used for follow up of treatment**

Scheme for diagnosis



Rapid Ab detection test

+ ve

-ve → **No infection**

Doesn't differentiate between **Current** (acute or chronic) inf. or **resolved** (cured or past) inf. or **False +ve** (no infection)

RT-PCR

+ve

Current infection

(Active viral replication either acute or chronic inf.)

Need for treatment

Monitor success of treatment by

Quantitative PCR

-ve → **No current infection**

2nd Ab confirmatory test

+ve

Cured (past) infection

-ve

False +ve rapid test

(No infection)

Mention the nature of the different hepatitis viruses

Hepatitis B Virus (HBV)

Structure

A-Core

1-Genome : Partially dsDNA.

2- DNA polymerase enzyme

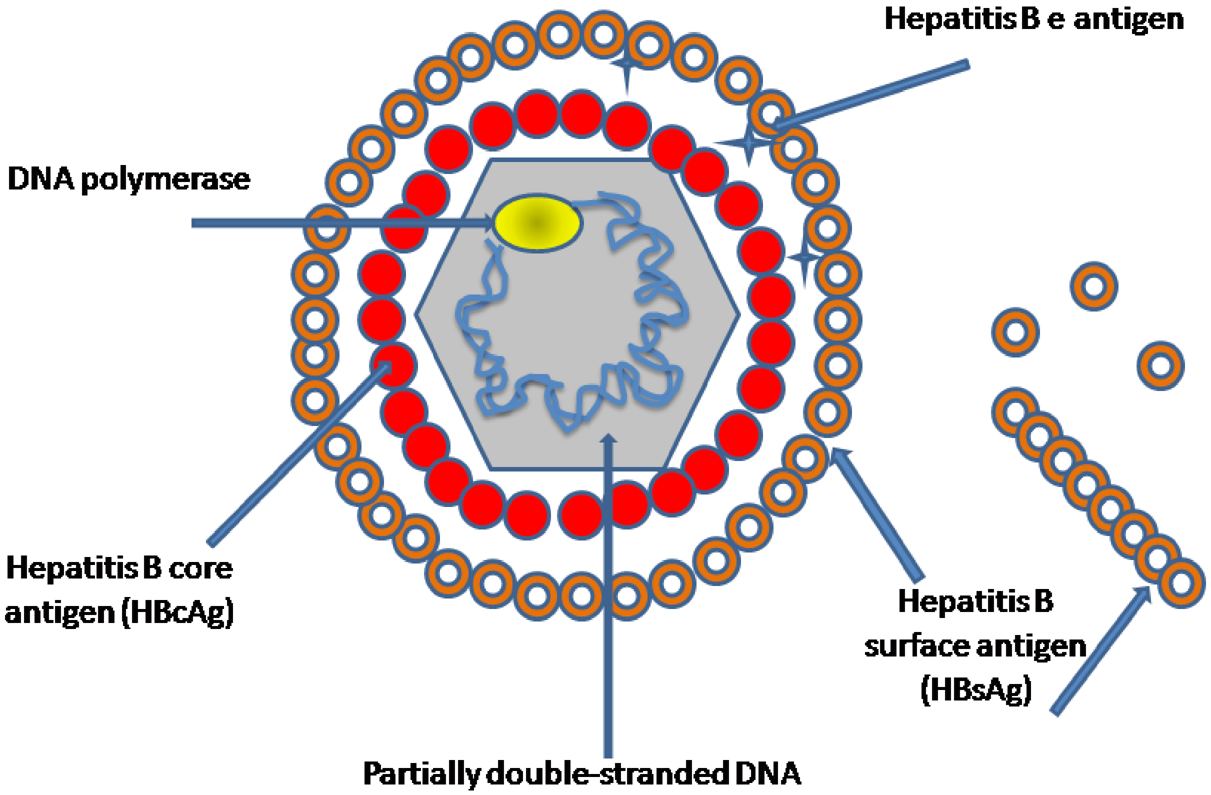
3-Ags

i. c (core) Ag

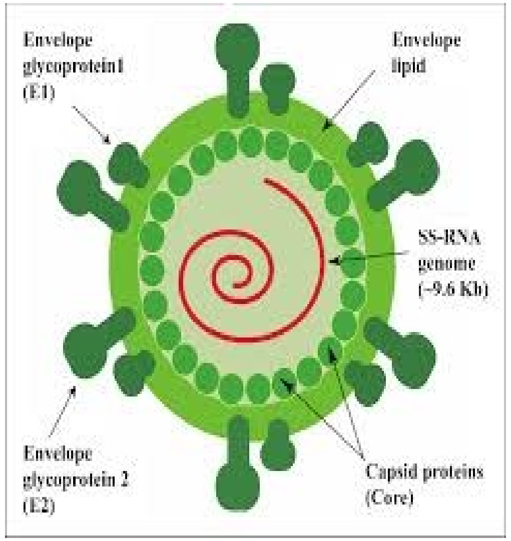
ii. e (early) Ag

B-Envelope

Host derived lipid part carrying **s (surface) Ag**


Hepatitis B e antigen
DNA polymerase
Hepatitis B core antigen (HBcAg)
Hepatitis B surface antigen (HBsAg)
Partially double-stranded DNA

Hepatitis C Virus (HCV)



A-Core

1-Genome : ssRNA

There are 6 genotypes based on differences in gene coding one of the 2 envelope glycoproteins (E2). Genotype 4 is predominant in Egypt, followed by type 1. (Higher resistance to antiviral drugs than other

How can virus C attack the liver?

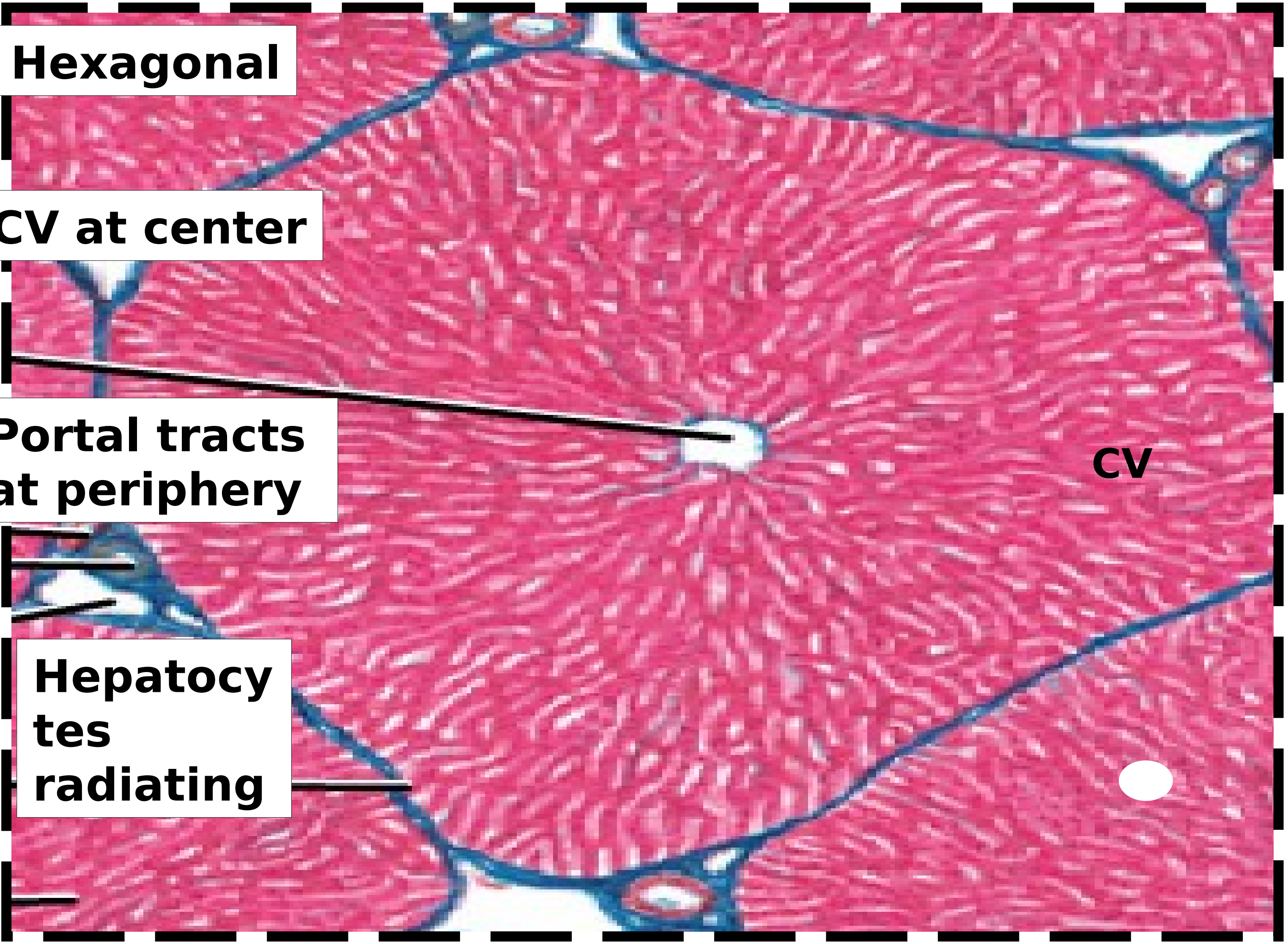
HCV:

- **Doesn't integrate into hepatocyte chromosomes.**
- **Response is primarily a T-cell mediated reaction, leading to damage of hepatocytes by T-cytotoxic cells**
- **During replication HCV proteins interact with many host cell factors involved in a wide range of activities, as cell cycle regulation, cell growth promotion, leading to possible carcinogenesis**

What is the normal structure of the liver?

Mention the arrangement of hepatocytes, name of cells lining the sinusoids and in the space of Disse

Classic hepatic lobule

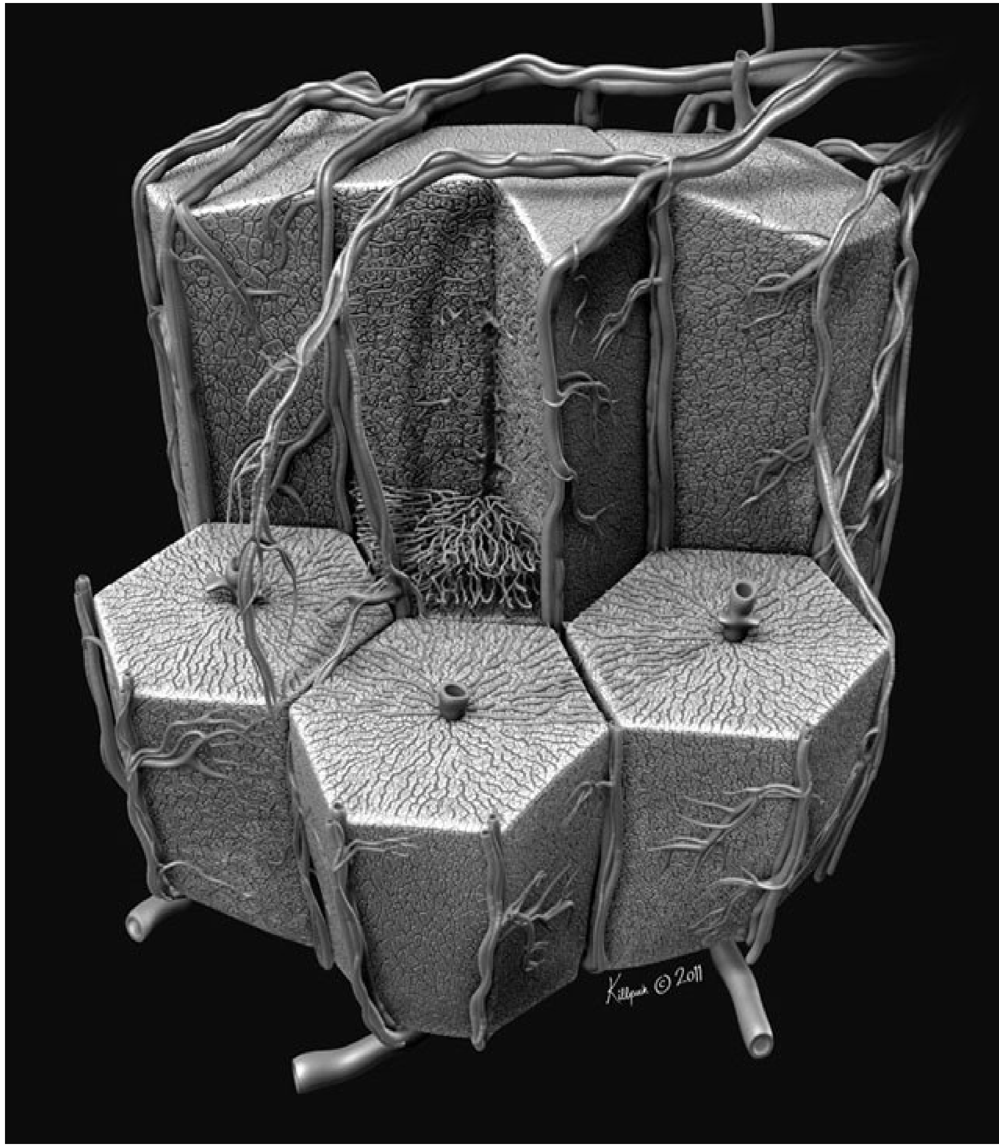


Hexagonal

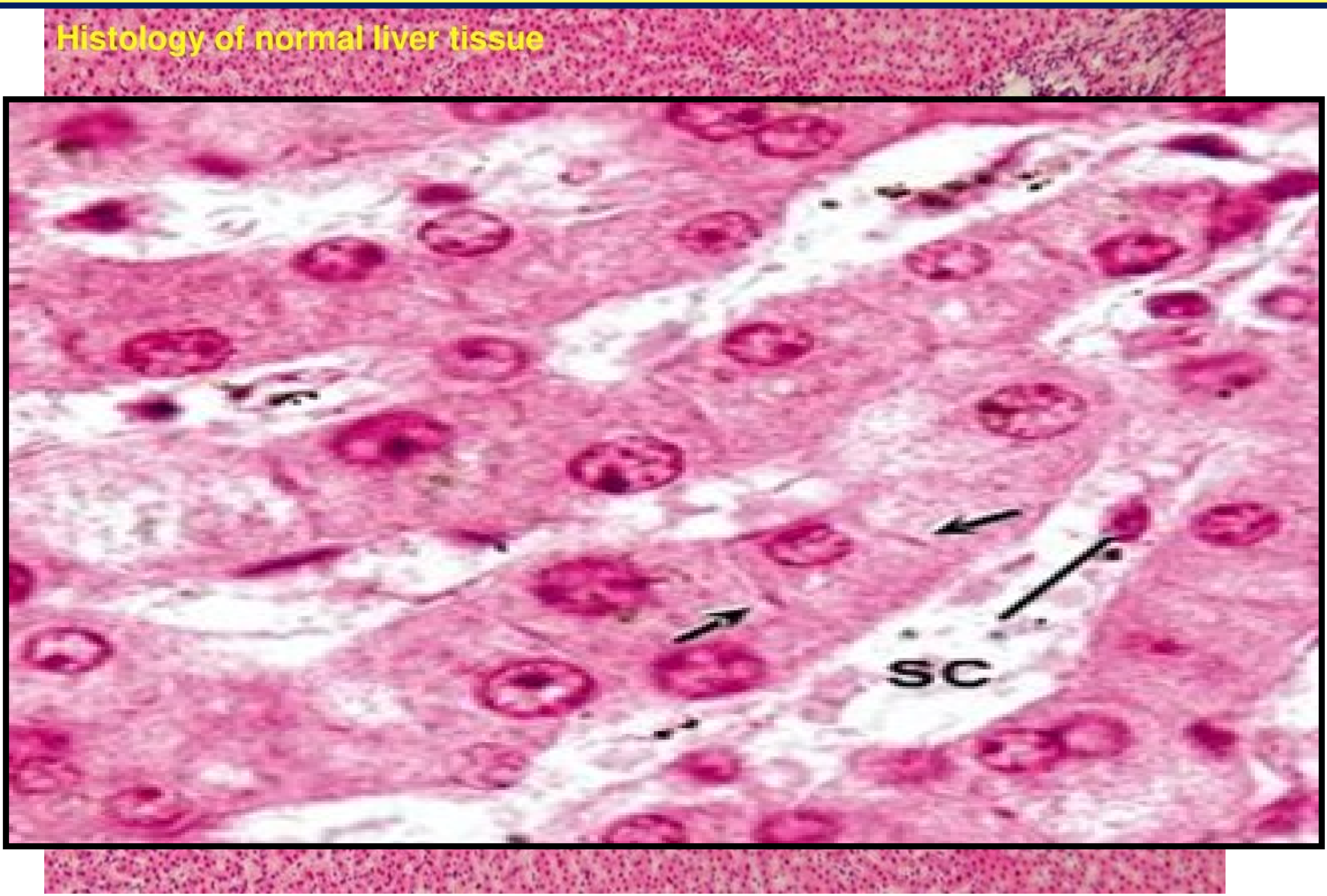
CV at center

Portal tracts at periphery

Hepatocytes radiating



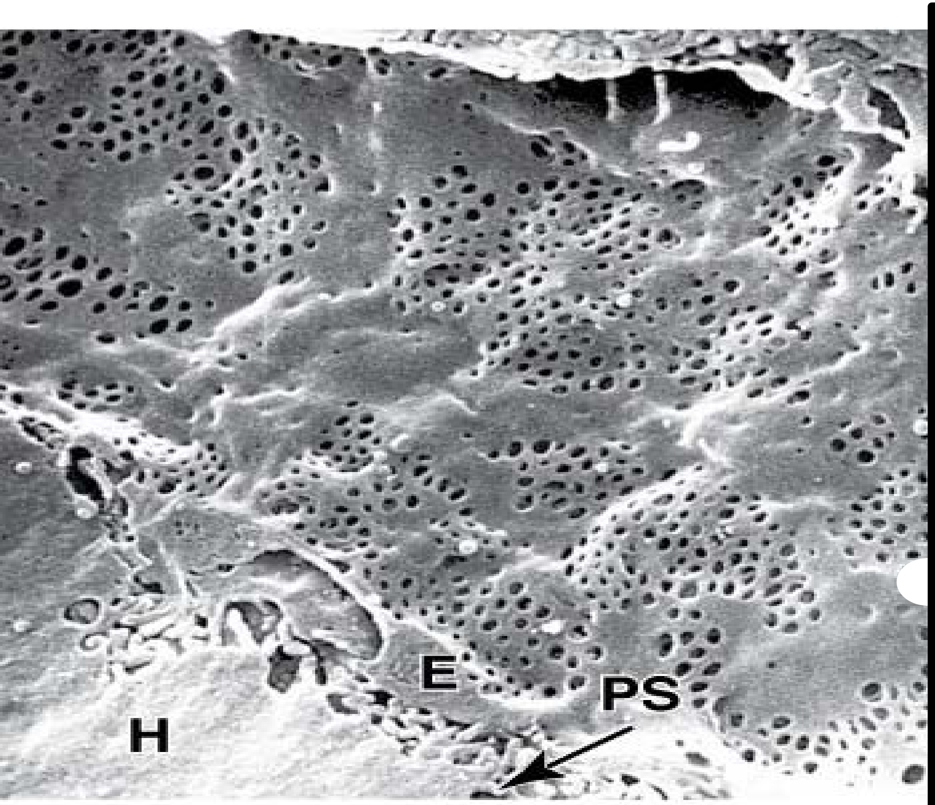
Liver - Hepatocytes



Blood sinusoids are lined by:

Endothelial cell

Von Kuppfer cell



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition*: http://www.accessmedicine.com

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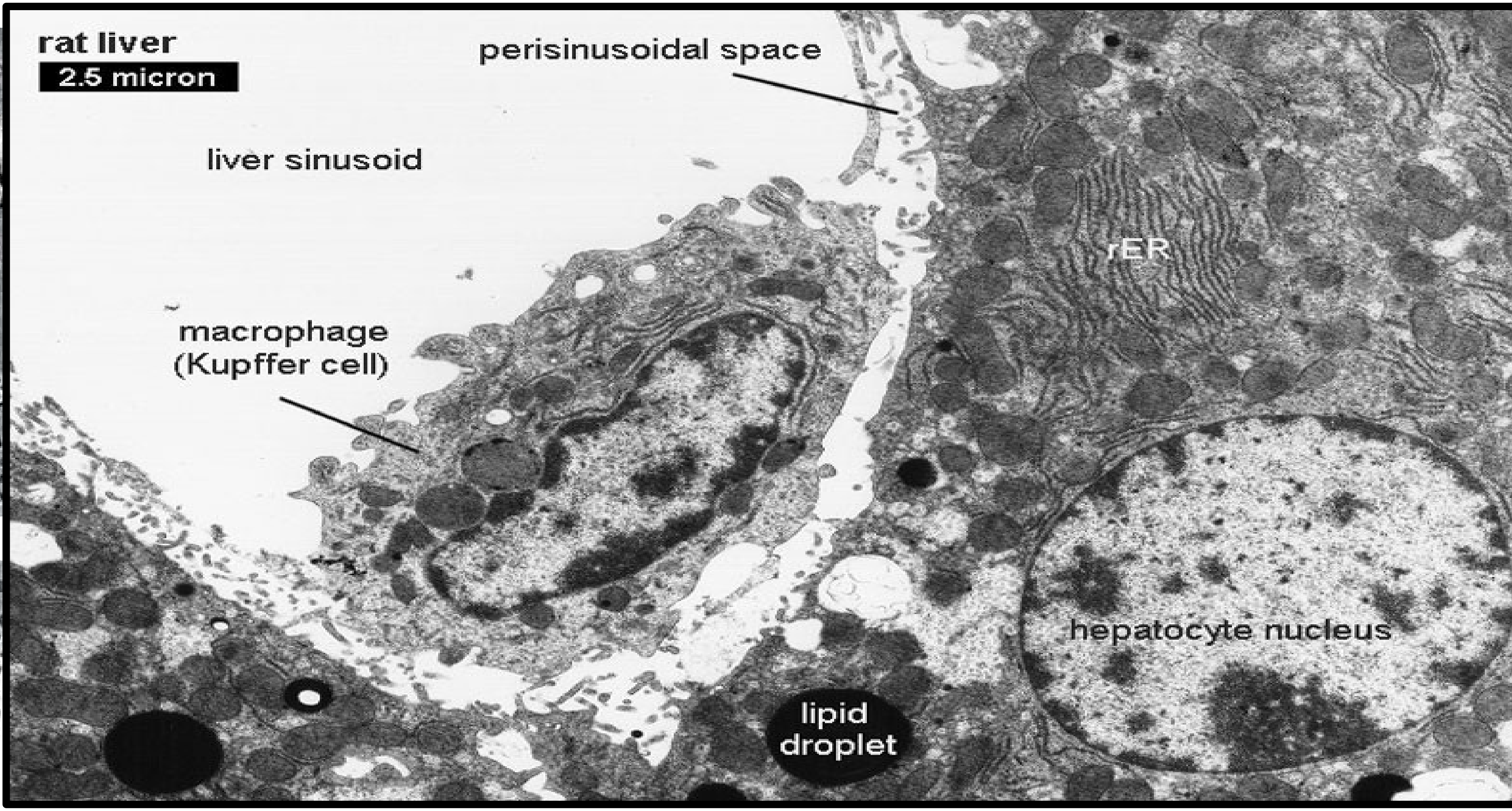
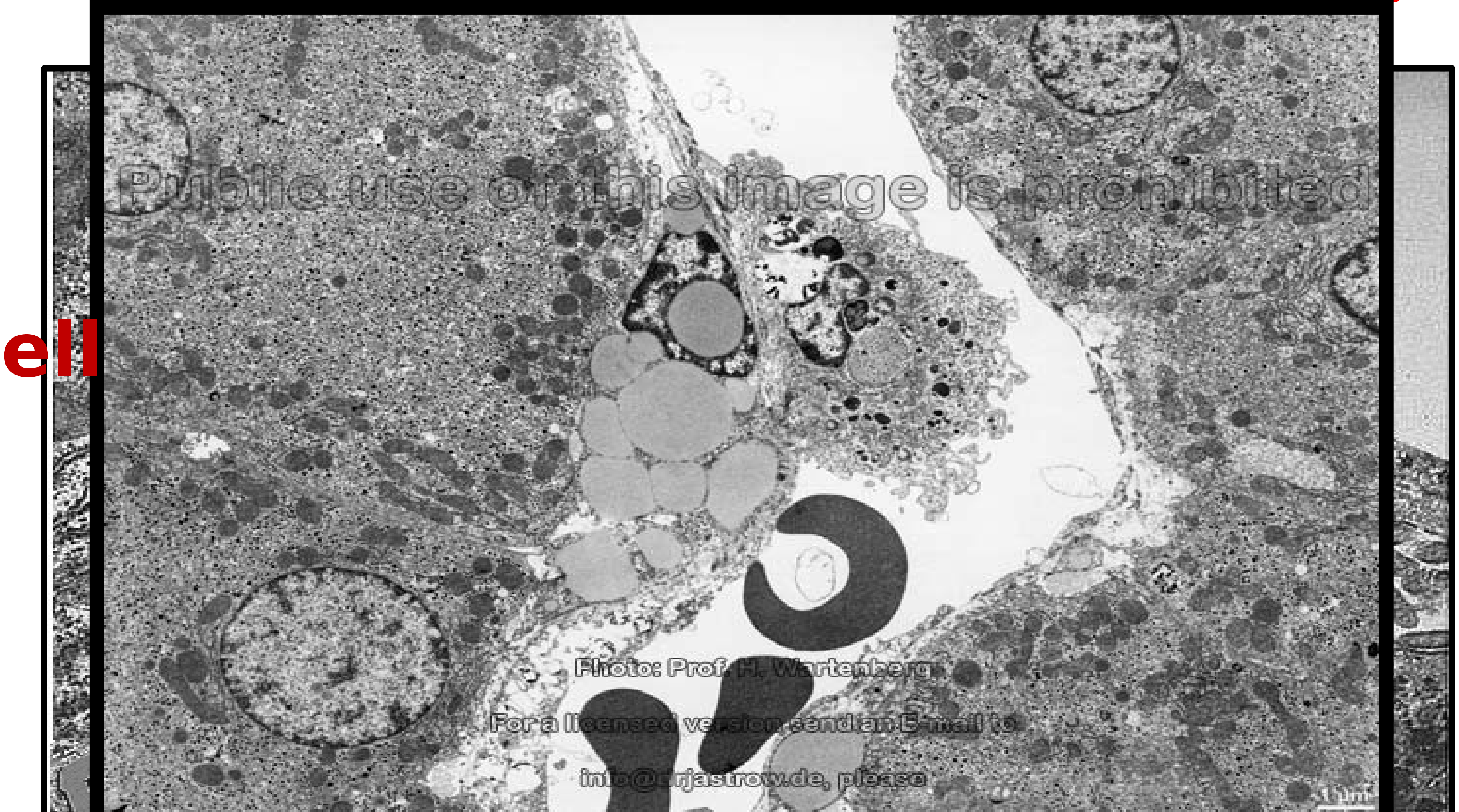


What is the space of Disse?

- It is the space between the hepatocytes and sinusoidal wall.
- It contains: -   -Microvilli from the hepatocytes - Plasma.

-Reticular fibers Occasional nerve fibers. -Ito cells (fat storing) .

Ito Cell



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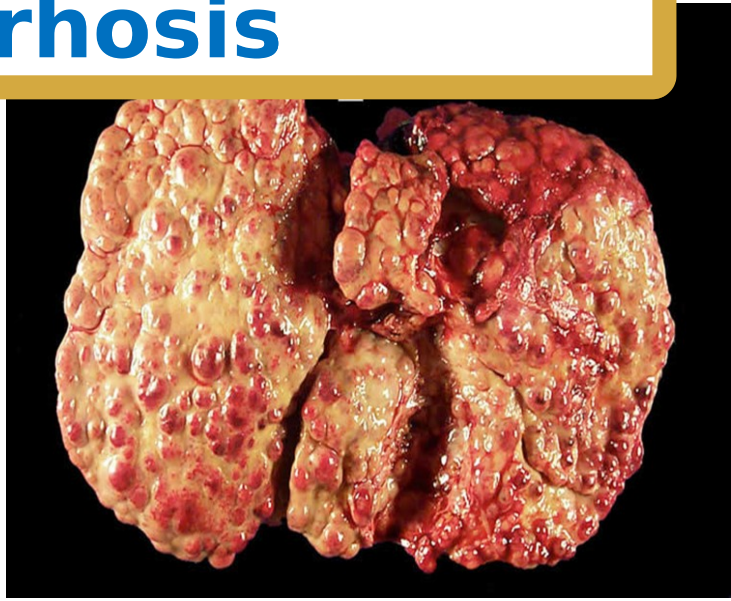
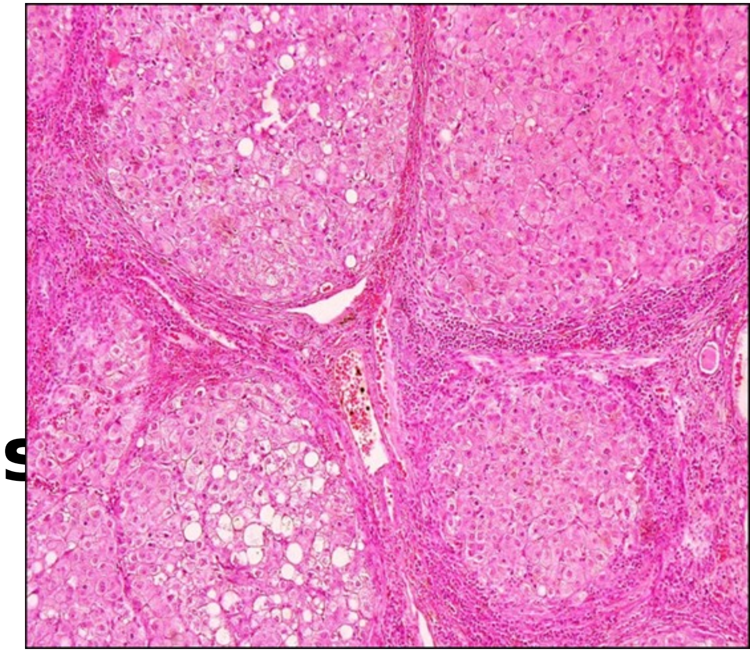
9- What are the pathological changes expected to be seen in the liver?

Pathologic Changes of Cirrhosis



Gross :

- Nodular outer and cut surface
- Nodules surrounded by fibrous septae



Mic :

- Parenchymal nodules of regenerating hepatocytes
- Surrounded by fibrous septae

NB :Features suggestive of viral Hepatitis C (in chronic hepatitis)

  - Steatosis
  - Portal lymphocytic infiltration +/-

What is the mechanism of cirrhosis of the liver?

Pathogenesis of Cirrhosis

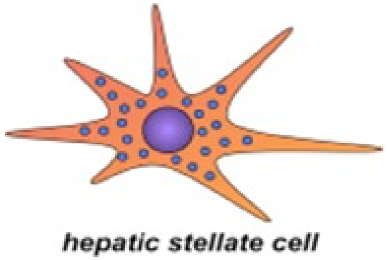
1-Hepatocyte death 2 -ECM deposition

Chronic inflammatory cells

Injured Cells: hepatocytes, endothelial & Kupffer cells

Increase Cytokines & growth factors

Perisinusoidal Stellate Cells (Ito cells)



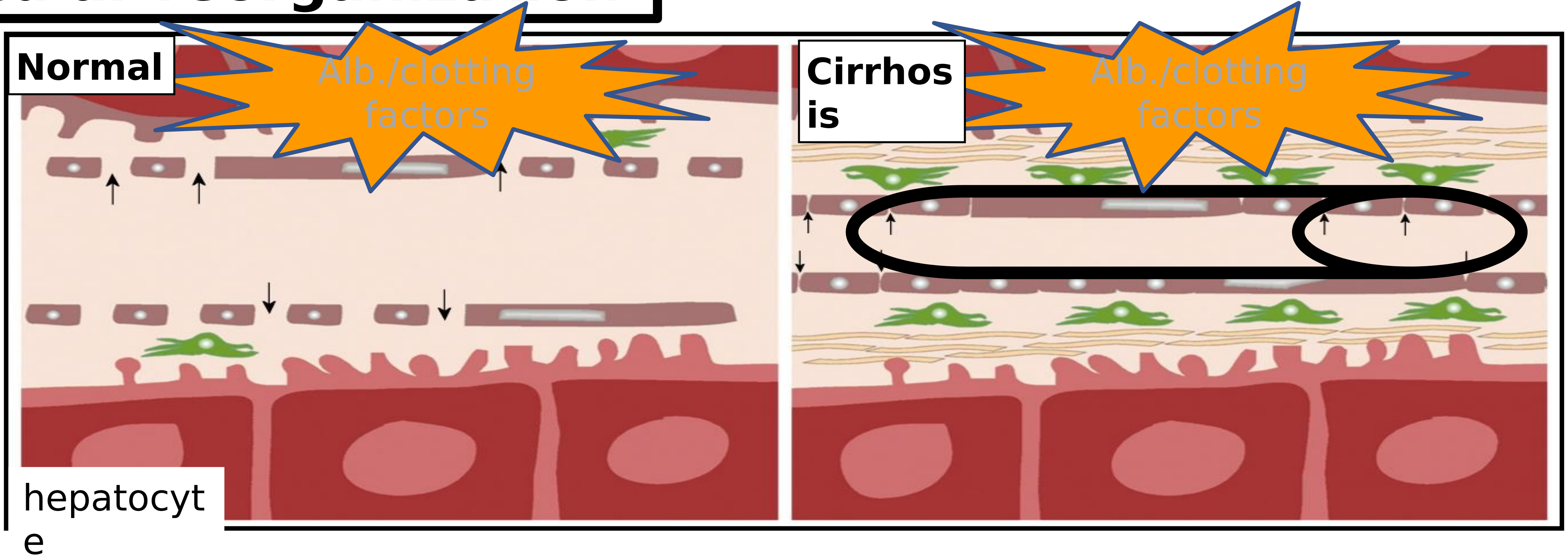
Myofibroblast

Collagen deposition & ECM

nodule formation

Pathogenesis of Cirrhosis

3-Vascular reorganization.



- Collagen deposition leads to loss of sinusoidal endothelial cell fenestrations
- Conversion of sinusoids **to higher pressure**, fast-vascular channels **without solute exchange** e.g., albumin, clotting factors

What is the general management of Laila?

- Non pharmacological: **low fat low salt diet.**
- Pharmacological: **DDAs** for ttt of HCV.
- Management of complications: ascites, jaundice, encephalopathy.
- Liver transplantation.
- Screening for HCC.
- Screening for varices.

Treatment

- Direct acting antiviral treatment:

Sofosbuvir 400 mg /day + **daclatasvir** 60 mg / day for 12 weeks

Sofosbuvir 400 mg /day + **Ledipasavir** mg/ day for 12 we

Sofosbuvir 400 mg / day + **Velpatasvir** / day for 12 wks

NDC 61958-1501-1
28 tablets
Sovaldi™
(sofosbuvir) Tablets
400 mg
Note to pharmacist:
Do not cover ALERT box with pharmacy label.
ALERT: Find out about medicines that should NOT be taken with Sovaldi™

10- What are the possible scenarios of prognosis in Laila?

- **Stationary course** with treatment

- Expected to see more complication of liver cirrhosis:

  -**Vascular decompensation**: Portal hypertension and variceal bleeding.

  -**Parenchymatous decompensation**: Ascites, jaundice, encephalopathy, liability for infection, SBP, HCC, HRS.

11- What are the complications expected to occur to Laila if not properly treated?

Complications of Cirrhosis

1. **Portal hypertension leading to**
   - **a.Ascites**
   - **b.Splenomegaly> hypersplenism> pancytopenia**
   - **c.Opening of Portosystemic sh**
     - **Esophageal varices**
     - **Piles**
     - **Caput medusa**
2. **Edema**
3. **Bleeding tendency**
4. **Failure of inactivation of oestrogen**
   - ➢**Amenorrhea**
   - ➢**Spider nevi - Palmar erythema**
5. **Hepatic failure & encephaopathy**
6. **Hepatocellular carcinoma**

- **Clinical presentation of liver cirrhosis is highly variable**
- ***If symptoms appear, they are non-specific***
- ***Screening of blood donors for viruses***
- ***Guidelines and evidence-based medicine***

Thank you